UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/595,580	06/15/2000	Edward R. Dougherty	4239-54279	9988

7590 02/27/2003

Klarquist Sparkman Campbell Leigh & Whinston LLP
One World Trade Center Ste 1600
121 S W Salmon St
Portland, OR 97204

EXAMINER
CLOW, LORI A

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/27/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/595,580	DOUGHERTY ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54 and 61-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54 and 61-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is further responsive to the amendment dated 14 August 2002 and supplemental to the Office Action dated 16 September 2002. This action supersedes the Office Action mailed 16 September 2002.

Claim Rejections - 35 USC § 112

Claims 1-54 and 61-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Firstly, as amended the claim 1 and claim 65, and dependent claims now include a method to quantify gene relatedness based upon data from a plurality of gene expression level observations from a permutation of the plurality of candidate genes. Applicant was asked to provide page and line number for support of the "permutation" language. The original claims read on effectiveness for the nonlinear model being measured and thereby quantifying gene relatedness. However, the amendments read on the effectiveness as a quantification of relatedness of genes rather than the effectiveness of the model as a whole and there is no basis for this in the specification. Furthermore, the support pointed to refers to permutations of predictive elements for the predicted gene and not a plurality of genes. There is no indication of what the permutations refer to in terms of gene expression. Applicant has also pointed to page 12, line 27-page 13, line 2 to explain quantification of effectiveness, further complicating the

issue of effectiveness of the model verses effectiveness of the relationship among expressed genes.

Secondly, as amended claim 50, and dependent claims, include "nonbinary" language. The support pointed to refers to a neural network-based nonlinear model. The example given refers to a ternary perceptron, which is not contemplated in the originally filed claims. A particular example does not give basis for a generic concept, just as reference to a particular compound in a class of compounds would not read on any compound from that class.

Thirdly, claim 54, and dependent claims include "a quantification as indicating relatedness". The specification does not provide information on assessing the quantification of the effectiveness of the model as it relates to gene relatedness. Rather, "the relatedness of the genes" is measured, without any step to provide how this translates to evaluation of the effectiveness of the overall model, as stated above.

Just because the genes can be labeled with a value indicating high, or low relatedness, does not give basis for the system to assess effectiveness of the model.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following constitutes a new grounds of rejection.

Claims 1-54 and 61-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (Journal of Biomedical Optics (1997) vol. 2:364-373: PTO-1449 reference) in view of Jian et al. (IEEE Transactions on Pattern Analysis and Machine Intelligence (2000) vol. 22:4-37: PTO-1449 reference)

As applied to claim 1 and related claims, Chen et al. disclose that the technology of microarray analysis is particularly useful for direct comparisons of mRNA levels from various cell types (page 365). This requires the ability to discern subtle changes in expression levels. This is best accomplished by pixel selection methods based on the Mann-Whitney test (page

368). The three points to this test are: (1) association of confidence levels with every intensity measurement based upon significance; (2) real-time measurements; and (3) lack of need for normality assumptions. In essence, data is randomly generated over the set of possible data. This reveals relationships between gene positions on the microarray (as described in detail on page 368). Target are aligned, averaged, and subjected to a threshold. After several iterations of these permutations, the result is deemed a site of significance. Once gene expression is established, expression ratios are determined for the differing samples or sets of genes. Finally, ratios are analyzed via statistical means (generation of confidence levels etc.) in order to obtain a satisfactory result. To verify this result, the method of K clustering is used (as described in Chen et al. (Proc. SPIE (1999) vol.3602:422-428; PTO-1449 reference). Chen et al. disclose a method of clustering genes based upon gene expression in order to identify functional relationships between the genes of interest (see abstract, page 422). This method utilizes cDNA microarrays and and is performed on a computer. "Gene expression patterns for a given biological process for a plurality of inputs representing expression at different time points are obtained ($i=1, 2, ...n$). Each gene pattern consists of expression ratios from m genes. The gene expression ration vector (m) contains n components. Therefore, the expression vectors must be partitioned into K clusters ($C_1, C_2, ...C_k$), such that cluster C_j contains m_j genes and each gene is in exactly one cluster." (page 423, point 2.) This is put simply on page 424, which explains the preparation and partitioning of gene expression data. This model is applied to gene expression data conducted in yeast (*S. cerevisiae*) containing 6400 distinct cDNA. Genes with no significant expression level changes were eliminated form the study, because they are usually housekeeping genes that do not respond to experimental manipulations or they are genes that cannot be

detected in microarray systems. Other systems were tested, as well, using the similar clustering approach as for the yeast (multidimensional scaling analysis) to establish relatedness amongst different gene expression patterns. This approach is certainly applicable to a variety of inputs that serve as predictors for the method. These could include particular cell states, as well as external stimuli, as is well known in the art of microarray analysis (differential displays etc...) (see page 422, introduction, 3rd paragraph). This method can be used with a plurality of predictive inputs, representative of differential expression between two or more samples of biological material and this can be done to compare predicted to observed levels (page 423, study example, top of page). Furthermore, the study shows that this method is useful for not only tens of thousands of genes, but also useful for a subset of those genes (a fingerprint). Another important factor in this method is that these levels of expression are statistically analyzed to give the "best" prediction possible across a set of biological samples (page 423, 2nd paragraph).

The above analysis of microarray gene expression based upon comparisons between pluralities of gene expression patterns can be useful in the prediction of gene relatedness when incorporating neural network technology (claims 20 and related claims), as taught by Jian et al. Jian et al. define "pattern" as consisting of two tasks: (1) supervised classification in which an input pattern is identified as a member of a predefined class and (2) unsupervised classification (e.g. clustering) in which the pattern is assigned to a hitherto unknown class. The four known approaches to pattern recognition are: (1) template matching, (2) statistical classification, (3) syntactic or structural matching, and (4) neural networks. These models are not necessarily independent (page 5). The definitions of the above four are well known in the art.

In the instant application, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Chen et al. with neural network technology, as described in Jian et al. As Jian states, the most common neural network system for pattern classification is the feed-forward network, which includes multiplayer perceptron and Radial-Basis Function (page 7). These provide a suite of nonlinear algorithms for feature extraction and classification. In addition, these feature extractions and classifications can be mapped on neural architectures. Inherent in neural networking is the use of statistical pattern recognition calculations, which are usually hidden from the user (internal manipulations). It is well known in the art that neural networks consist of a test pattern and a training pattern, meeting all of the limitations of the instant claims. For instance in the training mode, the feature extraction/selection module finds the appropriate features (like gene expression patterns) for representing the input patterns and the classifier is trained to partition the feature space. In the classification mode, the trained classifier assigns the input pattern to one of the pattern classes under consideration based upon measured features (page 8), as outlined in the instant application. Without further describing the vast information available in the field of neural networks, the motivation to analyze gene expression patterns is clearly put forth in Chen et al. (Proc SPIE) on page 425 in which they state, "expression clustering results provide group statistical information which may ultimately lead biologists to better understanding of the gene functional behavior during a given biological process....The future research work will certainly include an implementation combined with the gene expression database connection....in order to provide more efficient way towards unknown gene understanding."

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday-Friday from 10am to 6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER
~~GROUP 1800~~
AU1631

February 20, 2003

Lori A. Clow, Ph.D.
Art Unit 1631
Lori A. Clow